

Sandoz—Cont.**ADVERSE REACTIONS****Frequently Observed**

The most frequently reported adverse reactions are drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, abdominal pain, and intoxicated feeling.

Infrequently Observed

All adverse events tabulated below are classified as infrequent.

Central Nervous: headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot spells, numbness, sluggishness, seizure. Mental confusion, excitement or depression can also occur due to intolerance, particularly in elderly or debilitated patients, or due to overdosage of butalbital.

Autonomic Nervous: dry mouth, hyperhidrosis.

Gastrointestinal: difficulty swallowing, heartburn, flatulence, constipation.

Cardiovascular: tachycardia.

Musculoskeletal: leg pain, muscle fatigue.

Genitourinary: diuresis.

Miscellaneous: pruritus, fever, earache, nasal congestion, tinnitus, euphoria, allergic reactions.

The following adverse reactions have been voluntarily reported as temporally associated with Fiorinal® with Codeine, a related product containing aspirin, butalbital, caffeine, and codeine.

Central Nervous: abuse, addiction, anxiety, disorientation, hallucination, hyperactivity, insomnia, libido decrease, nervousness, neuropathy, psychosis, sexual activity increase, slurred speech, twitching, unconsciousness, vertigo.

Autonomic Nervous: epistaxis, flushing, miosis, salivation.

Gastrointestinal: anorexia, appetite increased, diarrhea, esophagitis, gastroenteritis, gastrointestinal spasms, hiccup, mouth burning, pyloric ulcer.

Cardiovascular: chest pain, hypotensive reaction, palpitations, syncope.

Skin: erythema, erythema multiforme, exfoliative dermatitis, hives, rash, toxic epidermal necrolysis.

Urinary: kidney impairment, urinary difficulty.

Miscellaneous: allergic reaction, anaphylactic shock, cholangiocarcinoma, drug interaction with erythromycin (stomach upset), edema.

The following adverse drug events may be borne in mind as potential effects of the components of Fioricet® with Codeine. Potential effects of high dosage are listed in the OVERDOSAGE section.

Acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Caffeine: cardiac stimulation, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.

Codeine: nausea, vomiting, drowsiness, lightheadedness, constipation, pruritus.

Several cases of dermatological reactions, including toxic epidermal necrolysis and erythema multiforme, have been reported for Fioricet® (Butalbital, Acetaminophen, and Caffeine Tablets, USP).

DRUG ABUSE AND DEPENDENCE**Controlled Substance**

Fioricet® with Codeine is controlled by the Drug Enforcement Administration and is classified under Schedule III.

Abuse and Dependence**Codeine**

Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic medications.

Butalbital

Barbiturates may be habit-forming: Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1,500 mg. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than two-fold. As this occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a barbiturate is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and gradual withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withdrawal regimens. One method involves initiating treatment at the patient's regular dosage level and gradually decreasing the daily dosage as tolerated by the patient.

OVERDOSAGE

Following an acute overdosage of Fioricet® with Codeine, toxicity may result from the barbiturate, the codeine, or the acetaminophen. Toxicity due to the caffeine is less likely, due to the relatively small amounts in this formulation.

Signs and Symptoms

Toxicity from barbiturate poisoning include drowsiness, confusion, and coma; respiratory depression; hypotension; and hypovolemic shock. Toxicity from codeine poisoning includes the opioid triad of pinpoint pupils, depression of respiration, and loss of consciousness. Convulsions may occur. In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necroses, hypoglycemic coma, and thrombocytopenia may also occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48–72 hours post-ingestion. In adults hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams. Acute caffeine poisoning may cause insomnia, restlessness, tremor, and delirium, tachycardia, and extrasystoles.

Treatment

A single or multiple overdose with Fioricet® with Codeine is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended. Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Pressors should be avoided. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration. If renal function is normal, forced diuresis may aid in the elimination of the barbiturate. Alkalization of the urine increases renal excretion of some barbiturates, especially phenobarbital.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered.

If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone 0.4–2 mg is given parenterally. Since the duration of action of codeine may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, N-acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels 4 or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals. Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

Toxic doses (for adults)

Butalbital: toxic dose 1.0 g
(20 capsules of Fioricet® with Codeine)

Acetaminophen: toxic dose 10 g
(30 capsules of Fioricet® with Codeine)

Caffeine: toxic dose 1.0 g
(25 capsules of Fioricet® with Codeine)

Codeine: toxic dose 240 mg
(8 capsules of Fioricet® with Codeine)

DOSAGE AND ADMINISTRATION

One or 2 capsules every 4 hours. Total daily dosage should not exceed 6 capsules.

Extended and repeated use of this product is not recommended because of the potential for physical dependence.

HOW SUPPLIED**Fioricet® with Codeine Capsules**

Dark blue, opaque cap with a grey, opaque body. Cap is imprinted twice in light-blue with "FIORICET" and "CODEINE". Body is imprinted twice with four-head profile "SANDOZ" in red.

Bottle of 100 (NDC 0078-0243-05)

ControlPak® unit-dose package of 25; continuous reverse-numbered roll of sealed blisters (NDC 0078-0243-13).

Store and Dispense

Below 86°F (30°C); tight container.

[REV: APRIL 1993]

Shown in Product Identification Guide, page 30132801

FIORINAL®

(butalbital, aspirin, and caffeine)
Tablets/Capsules, USP

Caution: Federal law prohibits dispensing without prescription.

The following information is based on official labeling effect on August 1, 1996.

DESCRIPTION

Each Fiorinal® (butalbital, aspirin, and caffeine) Capsule for oral administration contains: butalbital 100 mg (Warning: May be habit-forming); aspirin, USP, 40 mg.

Butalbital, 5-allyl-5-isobutyl-barbituric acid, has an empirical formula of $C_{11}H_{16}N_2O_3$ and a molecular weight of 212.16.

Aspirin, benzoic acid, 2-(acetoxy), has an empirical formula of $C_9H_8O_4$ and a molecular weight of 180.18.

Caffeine, 1, 3, 7-trimethylxanthine, has an empirical formula of $C_8H_{10}N_4O_2$ and a molecular weight of 164.19.

Tablets

Active Ingredients: aspirin, USP, butalbital, USP, and caffeine, USP.

Inactive Ingredients: alginic acid, lactose, microcrystalline cellulose, povidone, stearic acid, and another ingredient.

Capsules

Active Ingredients: aspirin, USP, butalbital, USP, and caffeine, USP.

Inactive Ingredients: D&C Yellow #10, gelatin, micro-

line cellulose, sodium lauryl sulfate, starch, and talc. *May Also Include:* benzyl alcohol, butylparaben, colorants including FD&C Blue #1, FD&C Green #3, FD&C yellow #6, edetate calcium disodium, methylparaben, paraben, silicon dioxide, and sodium propionate.

CLINICAL PHARMACOLOGY

Pharmacologically, Fiorinal® (butalbital, aspirin, and caffeine) combines the analgesic properties of aspirin with the anxiolytic and muscle relaxant properties of butalbital. The clinical effectiveness of Fiorinal® (butalbital, aspirin, and caffeine) in tension headache has been established in double-blind, placebo-controlled, multi-clinic trials. A trial design study compared Fiorinal® (butalbital, aspirin, and caffeine) with each of its major components. This demonstrated that each component contributes to the efficacy of Fiorinal® (butalbital, aspirin, and caffeine). The treatment of the target symptoms of tension headache (ache pain, psychic tension, and muscle contraction in head, neck, and shoulder region). For each symptom in the symptom complex as a whole, Fiorinal® (butalbital, aspirin, and caffeine) was shown to have significantly superior effects to either component alone.

Pharmacokinetics

The behavior of the individual components is described below.

Aspirin

The systemic availability of aspirin after an oral dose is highly dependent on the dosage form, the presence of food, the gastric emptying time, gastric pH, antacid buffers, agents, and particle size. These factors affect not only the extent of absorption of total salicylates but more importantly the extent of absorption of salicylic acid prior to absorption.

During the absorption process and after absorption, aspirin is mainly hydrolyzed to salicylic acid and distributed to body tissues and fluids, including fetal tissues, bone, and the central nervous system (CNS). Highest concentrations are found in plasma, liver, renal cortex, and lung. In plasma, about 50–80% of the salicylic acid metabolites are loosely bound to plasma proteins. The clearance of total salicylates is subject to saturable kinetics; however, first-order elimination kinetics are a good approximation for doses up to 650 mg. The half-life for aspirin is about 12 minutes and for salicylic acid, 2–3 hours. The total salicylates is about 3.0 hours.

The elimination of therapeutic doses is through the kidneys, either as salicylic acid or other biotransformation products. The renal clearance is greatly augmented by alkalinization of urine as is produced by concurrent administration of bicarbonate or potassium citrate.

The biotransformation of aspirin occurs primarily in hepatocytes. The major metabolites are salicylic acid (75%), the phenolic and acyl glucuronides (15%), and gentisic and gentisuric acid (1%). The bioavailability of the aspirin component of Fiorinal® (butalbital, aspirin, and caffeine) is equivalent to that of a 500 mg tablet except for a slower rate of absorption. A peak concentration of 8.80 µg/mL was obtained at 40 minutes after a 500 mg tablet.

See OVERDOSAGE for toxicity information.

well absorbed from the gastrointestinal tract and distributed to most of the tissues in the body. In general, may appear in breast milk across the placental barrier. They are bound to plasma proteins to a varying degree and binding capacity as a function of lipid solubility.

Butalbital is primarily via the kidney (about 50% of the dose) as unchanged drug or metabolites. Half-life is about 35 hours. Urinary excretion of parent drug (about 3.6% of the dose), 5-isobutyrylpropyl barbituric acid (about 24% of the dose), 5-(3-hydroxy-2-methyl-1-propyl) barbituric acid (about 14% of the dose), products with the barbituric acid moiety conjugated with excretion of urea (about 14% of the dose) and unidentified materials. Of the material excreted in urine, 32% was conjugated.

The bioavailability of the butalbital component of Fiorinal® (butalbital, aspirin, and caffeine) is equivalent to that of a single tablet for a decrease in the rate of absorption. A maximum concentration of 2020 ng/mL is obtained at about 1.5 hours after a 100 mg dose.

Plasma protein binding of butalbital is 45% over a concentration range of 0.5–20 µg/mL. This falls within the plasma protein binding (20%–45%) reported for other barbiturates such as phenobarbital, pentobarbital sodium. The plasma-to-blood concentration ratio is almost unity indicating that there is no preferential distribution of butalbital into either plasma or blood

USAGE for toxicity information.

Butalbital, aspirin, and caffeine is rapidly absorbed and distributed to all tissues and fluids, including the CNS, fetal circulation, and breast milk.

Excreted rapidly through metabolism and excretion in urine. The plasma half-life is about 3.0 hours. Transformation prior to excretion results in amounts of 1-methyl-xanthine and 1-methyluric acid, 70% of the dose that has been recovered in urine was unchanged drug.

The bioavailability of the caffeine component for Fiorinal® (butalbital, aspirin, and caffeine) is equivalent to that of a single tablet for a slightly longer time to peak. A peak concentration of 1680 ng/mL was obtained in less than an hour after a 100 mg dose.

USAGE for toxicity information.

WARNINGS

Contraindications: Fiorinal® (butalbital, aspirin, and caffeine) is contraindicated for the symptom complex of tension (or muscle contraction) headache. Evidence supporting the efficacy and safety of Fiorinal® (butalbital, aspirin, and caffeine) in the treatment of multiple recurrent headaches is unavailable. Caution is required because butalbital is habit-forming and potentially abusable.

INDICATIONS

Fiorinal® (butalbital, aspirin, and caffeine) is contraindicated for the following conditions:

Hypersensitivity or intolerance to aspirin, caffeine, or butalbital.

With a hemorrhagic diathesis (e.g., hemophilia, thrombocytopenia, von Willebrand's disease, the coagulopathies, thrombasthenia and other ill-defined platelet dysfunctions, severe vitamin K deficiency, liver damage).

With the syndrome of nasal polyps, angioedema, hyporesponsiveness to aspirin or other nonsteroidal anti-inflammatory drugs. Anaphylactoid reactions have occurred in such patients.

With other serious gastrointestinal lesions.

With porphyria.

With a history of anaphylactic shock or allergic reactions. It should be ascertained whether the patient is allergic to aspirin, although a specific history may be lacking.

Bleeding can result from aspirin therapy in patients with ulcer or other gastrointestinal lesions, and with bleeding disorders. Aspirin administered may prolong the bleeding time. Butalbital is habit-forming and potentially abusable. Consequently, the use of Fiorinal® (butalbital, aspirin, and caffeine) is contraindicated. Results from epidemiologic studies have shown a correlation between aspirin and Reye's Syndrome. Fiorinal® (butalbital, aspirin, and caffeine) should not be used in administering this product to teenagers, with chicken pox or flu.

Usage: Fiorinal® (butalbital, aspirin, and caffeine) should be prescribed for certain special-risk patients such as those debilitated, and those with severe impairment of hepatic function, coagulation disorders, head in-

juries, elevated intracranial pressure, acute abdominal conditions, hypothyroidism, urethral stricture, Addison's disease, or prostatic hypertrophy.

Aspirin should be used with caution in patients on anticoagulant therapy and in patients with underlying hemostatic defects, and extreme caution in the presence of peptic ulcer. Precautions should be taken when administering salicylates to persons with known allergies. Hypersensitivity to aspirin is particularly likely in patients with nasal polyps, and relatively common in those with asthma.

Information for Patients

Patients should be informed that Fiorinal® (butalbital, aspirin, and caffeine) contains aspirin and should not be taken by patients with an aspirin allergy.

Fiorinal® (butalbital, aspirin, and caffeine) may impair the mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking Fiorinal® (butalbital, aspirin, and caffeine).

Alcohol and other CNS depressants may produce an additive CNS depression when taken with Fiorinal® (butalbital, aspirin, and caffeine) and should be avoided.

Butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests

In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions

The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.

In patients receiving concomitant corticosteroids and chronic use of aspirin, withdrawal of corticosteroids may result in salicylism because corticosteroids enhance renal clearance of salicylates and their withdrawal is followed by return to normal rates of renal clearance.

Fiorinal® (butalbital, aspirin, and caffeine) may enhance the effects of:

- Oral anticoagulants, causing bleeding by inhibiting prothrombin formation in the liver and displacing anticoagulants from plasma protein binding sites.
- Oral antidiabetic agents and insulin, causing hypoglycemia by contributing an additive effect, if dosage of Fiorinal® (butalbital, aspirin, and caffeine) exceeds maximum recommended daily dosage.
- 6-mercaptopurine and methotrexate, causing bone marrow toxicity and blood dyscrasias by displacing these drugs from secondary binding sites, and, in the case of methotrexate, also reducing its excretion.
- Non-steroidal anti-inflammatory agents, increasing the risk of peptic ulceration and bleeding by contributing additive effects.
- Other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Fiorinal® (butalbital, aspirin, and caffeine) may diminish the effects of:

Uricosuric agents such as probenecid and sulfapyrazone, reducing their effectiveness in the treatment of gout. Aspirin competes with these agents for protein binding sites.

Drug/Laboratory Test Interactions

Aspirin: Aspirin may interfere with the following laboratory determinations in blood: serum amylase, fasting blood glucose, cholesterol, protein, serum glutamic-oxaloacetic transaminase (SGOT), uric acid, prothrombin time and bleeding time. Aspirin may interfere with the following laboratory determinations in urine: glucose, 5-hydroxyindoleacetic acid, Gerhardt ketone, vanillylmandelic acid (VMA), uric acid, diacetic acid, and spectrophotometric detection of barbiturates.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Adequate long-term studies have been conducted in mice and rats with aspirin, alone or in combination with other drugs, in which no evidence of carcinogenesis was seen. No adequate studies have been conducted in animals to determine whether aspirin has a potential for mutagenesis or impairment of fertility. No adequate studies have been conducted in animals to determine whether butalbital has a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Usage in Pregnancy

Teratogenic Effects:

Pregnancy Category C. Animal reproduction studies have not been conducted with Fiorinal® (butalbital, aspirin, and caffeine). It is also not known whether Fiorinal® (butalbital, aspirin, and caffeine) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Fiorinal® (butalbital, aspirin, and caffeine) should be given to a pregnant woman only when clearly needed.

Nonteratogenic Effects:

Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital-containing drug during the last 2 months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital

5mg/kg, which was tapered without further seizure or other withdrawal symptoms.

Studies of aspirin use in pregnant women have not shown that aspirin increases the risk of abnormalities when administered during the first trimester of pregnancy. In controlled studies involving 41,337 pregnant women and their offspring, there was no evidence that aspirin taken during pregnancy caused stillbirth, neonatal death or reduced birth weight. In controlled studies of 50,282 pregnant women and their offspring, aspirin administration in moderate and heavy doses during the first four lunar months of pregnancy showed no teratogenic effect.

Therapeutic doses of aspirin in pregnant women close to term may cause bleeding in mother, fetus, or neonate. During the last 6 months of pregnancy, regular use of aspirin in high doses may prolong pregnancy and delivery.

Labor and Delivery

Ingestion of aspirin prior to delivery may prolong delivery or lead to bleeding in the mother or neonate.

Nursing Mothers

Aspirin, caffeine, and barbiturates are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from Fiorinal® (butalbital, aspirin, and caffeine), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequent adverse reactions are drowsiness and dizziness. Less frequent adverse reactions are lightheadedness and gastrointestinal disturbances including nausea, vomiting, and flatulence. A single incidence of bone marrow suppression has been reported with the use of Fiorinal® (butalbital, aspirin, and caffeine). Several cases of dermatological reactions including toxic epidermal necrolysis and erythema multiforme have been reported.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Fiorinal® (butalbital, aspirin, and caffeine) is controlled by the Drug Enforcement Administration and is classified under Schedule III.

Abuse and Dependence

Butalbital

Barbiturates may be habit-forming: Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1,500 mg. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than twofold. As this occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a barbiturate is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and gradual withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withdrawal regimens. One method involves initiating treatment at the patient's regular dosage level and gradually decreasing the daily dosage as tolerated by the patient.

OVERDOSAGE

The toxic effects of acute overdosage of Fiorinal® (butalbital, aspirin, and caffeine) are attributable mainly to its barbiturate component, and, to a lesser extent, aspirin. Because toxic effects of caffeine occur in very high dosages only, the possibility of significant caffeine toxicity from Fiorinal® (butalbital, aspirin, and caffeine) overdosage is unlikely.

Signs and Symptoms

Symptoms attributable to **acute barbiturate poisoning** include drowsiness, confusion, and coma; respiratory depression; hypotension; hypovolemic shock. Symptoms attributable to **acute aspirin poisoning** include hyperpnea; acid-base disturbances with development of metabolic acidosis; vomiting and abdominal pain; tinnitus; hyperthermia; hypoprothrombinemia; restlessness; delirium; convulsions. **Acute caffeine poisoning** may cause insomnia, restlessness, tremor, and delirium; tachycardia and extrasystoles.

Treatment

Treatment consists primarily of management of barbiturate intoxication and the correction of the acid-base imbalance due to salicylism. Vomiting should be induced mechanically or with emetics in the conscious patient. Gastric lavage may be used if the pharyngeal and laryngeal reflexes are present and if less than 4 hours have elapsed since ingestion. A cuffed endotracheal tube should be inserted before gastric

Continued on next page

Sandoz—Cont.

avage of the unconscious patient and when necessary to provide assisted respiration. Diuresis, alkalinization of the urine, and correction of electrolyte disturbances should be accomplished through administration of intravenous fluids such as 1% sodium bicarbonate in 5% dextrose in water. Meticulous attention should be given to maintaining adequate pulmonary ventilation. The value of vasopressor agents such as Norepinephrine or Phenylephrine Hydrochloride in treating hypotension is questionable since they increase vasoconstriction and decrease blood flow. However, if prolonged support of blood pressure is required, Norepinephrine Bitartrate (Levophed®)* may be given I.V. with the usual precautions and serial blood pressure monitoring. In severe cases of intoxication, peritoneal dialysis, hemodialysis, or exchange transfusion may be lifesaving. Hypoprothrombinemia should be treated with Vitamin K, intravenously.

Up-to-date information about the treatment of overdose can often be obtained from a Certified Regional Poison Control Center. Telephone numbers of Certified Regional Poison Control Centers are listed in the Physicians' Desk Reference®.**

Toxic and Lethal Doses

Butalbital: toxic dose 1.0 g (20 tablets/capsules of Fiorinal®)

Aspirin: toxic blood level greater than 30 mg/100 mL; lethal dose 10-30 g

Caffeine: toxic dose 1.0 g (25 tablets/capsules of Fiorinal®)

DOSAGE AND ADMINISTRATION

One or 2 tablets or capsules every 4 hours. Total daily dose should not exceed 6 tablets or capsules.

Extended and repeated use of this product is not recommended because of the potential for physical dependence.

HOW SUPPLIED

Fiorinal® (butalbital, aspirin, and caffeine)

Tablets/Capsules, USP

Tablets

White, round compressed tablet, engraved "FIORINAL" on one side, "SANDOZ" on other side.

Packages of 100 (NDC 0078-0104-05)

Packages of 1000 (NDC 0078-0104-09)

SandoPak® (unit-dose) package of 100 tablets individually blister-sealed (NDC 0078-0104-06)

Capsules

Bright kelly green cap with a lime green body, imprinted "FIORINAL 78-103" on each half of capsule.

Packages of 100 (NDC 0078-0103-05)

Packages of 500 (NDC 0078-0103-08)

ControlPak® package, 25 capsules (continuous, reverse-numbered roll of sealed blisters) (NDC 0078-0103-13)

Store and Dispense

Below 77°F (25°C), tight container.

*Levophed is a registered Trademark of Sanofi Winthrop Pharmaceuticals.

**Trademark of Medical Economics Data Production Company.

[REV: FEBRUARY 1996 30130903]

Shown in Product Identification Guide, page 333

FIORINAL® with CODEINE

[fe'-or-i-nol]

(butalbital, aspirin, caffeine, and codeine phosphate)

Capsules, USP

© R

CAUTION: Federal law prohibits dispensing without prescription.

The following prescribing information is based on official labeling in effect on August 1, 1996.

DESCRIPTION

Fiorinal® with Codeine (butalbital, aspirin, caffeine, and codeine phosphate) is supplied in capsule form for oral administration.

Each capsule contains:

codeine phosphate, USP 30 mg (1/2 gr)

Warning: May be habit-forming.

butalbital, USP 50 mg

Warning: May be habit-forming.

caffeine, USP 40 mg

aspirin, USP 325 mg

Codeine phosphate [morphine-3-methyl ether phosphate (1:1) (salt) hemihydrate, C₁₈H₂₄NO₂P, anhydrous mw 397.37], is a narcotic analgesic and antitussive.

Butalbital (5-allyl-5-isobutylbarbituric acid, C₁₁H₁₆N₂O₃, mw 224.26), is a short- to intermediate-acting barbiturate.

Caffeine (1,3,7-trimethylxanthine, C₈H₁₀N₄O₂, mw 194.19), is a central nervous stimulant.

Aspirin is benzoic acid, 2-(acetoxy)-C₉H₈O₄, mw 180.16, is an analgesic, antipyretic, anti-inflammatory.

Inactive Ingredients: D&C Yellow #10, FD&C Blue #1, FD&C Red #3, FD&C Yellow #6, gelatin, microcrystalline

cellulose, sodium lauryl sulfate, starch, talc, titanium dioxide.

May Also Include: benzyl alcohol, butylparaben, edetate calcium disodium, glycerin, methylparaben, propylparaben, silicon dioxide, sodium propionate.

CLINICAL PHARMACOLOGY

Fiorinal® with Codeine (butalbital, aspirin, caffeine, and codeine phosphate) is a combination drug product intended as a treatment for tension headache.

Fiorinal® (butalbital, aspirin, and caffeine) consists of a fixed combination of caffeine 40 mg, butalbital 50 mg, and aspirin 325 mg. The role each component plays in the relief of the complex of symptoms known as tension headache is incompletely understood.

Pharmacokinetics

Bioavailability: The bioavailability of the components of the fixed combination of Fiorinal® with Codeine (butalbital, aspirin, caffeine, and codeine phosphate) is identical to their bioavailability when Fiorinal® (butalbital, aspirin, and caffeine) and Codeine are administered separately in equivalent molar doses.

The behavior of the individual components is described below.

Aspirin

The systemic availability of aspirin after an oral dose is highly dependent on the dosage form, the presence of food, the gastric emptying time, gastric pH, antacids, buffering agents, and particle size. These factors affect not necessarily the extent of absorption of total salicylates but more the stability of aspirin prior to absorption.

During the absorption process and after absorption, aspirin is mainly hydrolyzed to salicylic acid and distributed to all body tissues and fluids, including fetal tissues, breast milk, and the central nervous system (CNS). Highest concentrations are found in plasma, liver, renal cortex, heart, and lung. In plasma, about 50%-80% of the salicylic acid and its metabolites are loosely bound to plasma proteins.

The clearance of total salicylates is subject to saturable kinetics; however, first-order elimination kinetics are still a good approximation for doses up to 650 mg. The plasma half-life for aspirin is about 12 minutes and for salicylic acid and/or total salicylates is about 3.0 hours.

The elimination of therapeutic doses is through the kidneys either as salicylic acid or other biotransformation products.

The renal clearance is greatly augmented by an alkaline urine as is produced by concurrent administration of sodium bicarbonate or potassium citrate.

The biotransformation of aspirin occurs primarily in the hepatocytes. The major metabolites are salicyluric acid (75%), the phenolic and acyl glucuronides of salicylate (15%), and gentisic and gentisuric acid (1%). The bioavailability of the aspirin component of Fiorinal® with Codeine (butalbital, aspirin, caffeine, and codeine phosphate) capsules is equivalent to that of a solution except for a slower rate of absorption. A peak concentration of 8.80 µg/mL was obtained at 40 minutes after a 650 mg dose.

See OVERDOSAGE for toxicity information.

Codeine

Codeine is readily absorbed from the gastrointestinal tract. It is rapidly distributed from the intravascular spaces to the various body tissues, with preferential uptake by parenchymatous organs such as the liver, spleen, and kidney. Codeine crosses the blood-brain barrier, and is found in fetal tissue and breast milk. The plasma concentration does not correlate with brain concentration or relief of pain, however, codeine is not bound to plasma proteins and does not accumulate in body tissues.

The plasma half-life is about 2.9 hours. The elimination of codeine is primarily via the kidneys, and about 90% of an oral dose is excreted by the kidneys within 24 hours of dosing. The urinary secretion products consist of free and glucuronide-conjugated codeine (about 70%), free and conjugated norcodeine (about 10%), free and conjugated morphine (about 10%), normorphine (4%), and hydrocodone (1%). The remainder of the dose is excreted in the feces.

At therapeutic doses, the analgesic effect reaches a peak within 2 hours and persists between 4 and 6 hours.

The bioavailability of the codeine component of Fiorinal® with Codeine (butalbital, aspirin, caffeine, and codeine phosphate) capsules is equivalent to that of a solution. Peak concentrations of 198 ng/mL were obtained at 1 hour after a 60 mg dose.

See OVERDOSAGE for toxicity information.

Butalbital

Butalbital is well absorbed from the gastrointestinal tract and is expected to distribute to most of the tissues in the body. Barbiturates, in general, may appear in breast milk and readily cross the placental barrier. They are bound to plasma and tissue proteins to a varying degree and binding increases directly as a function of lipid solubility.

Elimination of butalbital is primarily via the kidney (59%-88% of the dose) as unchanged drug or metabolites. The plasma half-life is about 35 hours. Urinary excretion products included parent drug (about 3.6% of the dose), 5-isobutyl-5-(2,3-dihydroxypropyl) barbituric acid (about 24% of

the dose), 5-allyl-5-(3-hydroxy-2-methyl-1-propyl) barbituric acid (about 4.8% of the dose), products with the barbituric acid ring hydrolyzed with excretion of urea (about 14% of the dose), as well as unidentified materials. Of the material excreted in the urine, 32% was conjugated.

The bioavailability of the butalbital component of Fiorinal® with Codeine (butalbital, aspirin, caffeine, and codeine phosphate) capsules is equivalent to that of a solution except for a decrease in the rate of absorption. A peak concentration of 2020 ng/mL is obtained at about 1.5 hours after a 100 mg dose.

The *in vitro* plasma protein binding of butalbital is 45% in the concentration range of 0.5-20 µg/mL. This falls within the range of plasma protein binding (20%-45%) reported with other barbiturates such as phenobarbital, pentobarbital, and secobarbital sodium. The plasma-to-blood concentration ratio was almost unity indicating that there is no preferential distribution of butalbital into either plasma or red blood cells.

See OVERDOSAGE for toxicity information.
Caffeine

Like most xanthines, caffeine is rapidly absorbed and distributed in all body tissues and fluids, including the CNS and bone marrow. Caffeine is cleared rapidly through metabolism and excretion in the urine. The plasma half-life is about 3 hours. Hepatic biotransformation prior to excretion results in about equal amounts of 1-methyl-xanthine and 1-methyluric acid. Of the 70% of the dose that has been recovered in the urine, only 3% was unchanged drug.

The bioavailability of the caffeine component for Fiorinal® with Codeine (butalbital, aspirin, caffeine, and codeine phosphate) capsules is equivalent to that of a solution except for a slightly longer time to peak. A peak concentration of 1660 ng/mL was obtained in less than an hour for an 80 mg dose.

See OVERDOSAGE for toxicity information.

INDICATIONS

Fiorinal® with Codeine (butalbital, aspirin, caffeine, and codeine phosphate) is indicated for the relief of the symptoms of tension (or muscle contraction) headache. Evidence supporting the efficacy of Fiorinal® with Codeine (butalbital, aspirin, caffeine, and codeine phosphate) capsules was derived from 2 multi-clinic trials that compared patients with tension headache randomly assigned to 4 parallel treatments: Fiorinal® with Codeine (butalbital, aspirin, caffeine, and codeine phosphate), codeine, Fiorinal® (butalbital, aspirin, and caffeine), and placebo. Response was assessed over the course of the first 4 hours of each of 2 distinct headache attacks separated by at least 24 hours. Fiorinal® with Codeine (butalbital, aspirin, caffeine, and codeine phosphate) was approved statistically significantly superior to each of its components (Fiorinal®, codeine) and to placebo on measures of pain relief.

Evidence supporting the efficacy and safety of Fiorinal® with Codeine (butalbital, aspirin, caffeine, and codeine phosphate) in the treatment of multiple recurrent headache is unavailable. Caution in this regard is required because codeine and butalbital are habit-forming and potentially abusive.

CONTRAINDICATIONS

Fiorinal® with Codeine (butalbital, aspirin, caffeine, and codeine phosphate) is contraindicated under the following conditions:

1. Hypersensitivity or intolerance to aspirin, caffeine, butalbital or codeine.
2. Patients with a hemorrhagic diathesis (e.g., hemophilia, hypoprothrombinemia, von Willebrand's disease, thrombocytopenias, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage.)
3. Patients with the syndrome of nasal polyps, angioneurotic edema and bronchospastic reactivity to aspirin or other NSAIDs, and steroid anti-inflammatory drugs. Anaphylactic reactions have occurred in such patients.
4. Peptic ulcer or other serious gastrointestinal lesions.
5. Patients with porphyria.

WARNINGS

Therapeutic doses of aspirin can cause anaphylactic shock and other severe allergic reactions. It should be ascertained if the patient is allergic to aspirin, although a specific history of allergy may be lacking.

Significant bleeding can result from aspirin therapy in patients with peptic ulcer or other gastrointestinal lesions, particularly in patients with bleeding disorders.

Aspirin administered pre-operatively may prolong the bleeding time.

In the presence of head injury or other intracranial lesion, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their cardiovascular effects for elevating cerebrospinal fluid pressure. Narcotics such as dextroamphetamine (SG) produce other CNS depressant effects, such as drowsiness, which may further obscure the clinical course of patients with head injuries.